and physical activity can have profound effects on the proliferation of NG2$^+$ glia[2]. Injury causes these cells to cycle much more rapidly, whereas physical activity causes them to almost immediately exit the cell cycle and differentiate into mature oligodendrocytes[2]. Thus, some of the activity-dependent regulation of NG2$^+$ glial proliferation may indeed continue into adulthood.

The adaptive behavior of NG2$^+$ glia as oligodendrocyte progenitors suggests that they might act as the crucial link between neuronal activity and the physiologically appropriate extent of myelination. Accordingly, synaptic communication between neurons and NG2$^+$ glia has been implicated in remyelination[9], although there is no direct evidence of this. Notably, NG2$^+$ cells lose their synapses as they differentiate into mature oligodendrocytes[10], which is consistent with neuronal input regulating their proliferation and differentiation rate. Electrical activity has long been known to influence myelination, and glutamate or ATP released by neurons inhibits the proliferation and differentiation of oligodendrocyte progenitors, which is consistent with a direct influence of neurotransmitters on NG2$^+$ cell cycle regulation (for review, see ref. 11). Is the regulation of NG2$^+$ glial proliferation in the barrel cortex linked to myelination processes? Although Mangin *et al.*[5] do not directly address this, it is interesting to note that fibers in the barrel walls are less innervated, but more myelinated, than those in the barrel cores[12], which is consistent with the idea that higher numbers of NG2$^+$ glia translate at some point into increased myelination. This is an intriguing finding in regard to other sensory circuits, such as those in the auditory system, that must push conduction velocity and exact timing to the limits[13]. The manner in which these circuits may adapt myelination to their needs remains an open question.

The relevance of adapting NG2$^+$ glia numbers to regulate myelination also extends to the adult brain. Is the continued presence of a source of oligodendrocyte progenitors in the adult brain, the NG2$^+$ glia, a prerequisite for the continued, albeit reduced, plasticity in some brain regions, such as the adult cerebral cortex? As mentioned above, contrary to the assumption that the end of the critical period correlates to the end of myelination, it is now clear that both processes continue into adulthood, but how they are linked has not yet been addressed. Notably, proliferation of NG2$^+$ glia has also been observed in the human brain[14], and extensive practicing of a task, such as playing the piano, seems to correlate with increased white matter, which is suggestive of increased myelination[15]. Thus, the work by Mangin *et al.*[5] in the neonatal barrel cortex prompts the exciting hypothesis that, in the adult brain too, synaptic input onto NG2$^+$ glia may act to improve neural circuits by modulating myelination and hence conduction velocity and/or timing. Understanding this link and hence the regulation of NG2$^+$ glial proliferation and behavior will therefore be important, not only for understanding the optimization of neural circuits during development but also for improving their plasticity and performance after injury.

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Bursting for exploration

Joaquim Alves da Silva & Rui M Costa

Phasic bursting of dopaminergic neurons influences many behaviors. A study now finds that ATP-sensitive potassium channels mediate bursting in dopaminergic neurons of the medial substantia nigra and affect novelty-induced exploration.

Being able to explore a new environment, learn from reinforcement, initiate movements and track time is essential for survival. Although these aptitudes are apparently different, the dopaminergic system has been implicated in all of them[1–3]. Nevertheless, it is not completely clear whether different dopaminergic neurons or distinct processes in these neurons are differentially involved in these functions. In this issue, Schiemann *et al.*[4] show that ATP-sensitive potassium (K-ATP) channels are responsible for the distinctive firing patterns of a specific subset of dopaminergic neurons, as well as for modulating novelty-induced exploration.

Dopaminergic neurons in the midbrain are mainly organized into two nuclei, the ventral tegmental area (VTA) and the substantia nigra pars compacta (SN). These neurons have typical firing patterns that are characterized by spontaneous low-frequency spikes[5]. Dopaminergic neurons can also show bursts of higher frequency firing[6]. For example, dopaminergic neurons can fire bursts in response to unexpected rewards or reward-predicting stimuli[1], or during the initiation or termination of action sequences[2]. Schiemann *et al.*[4] found that neurons from the medial portion of the SN (m-SN) have different bursting properties than those in VTA and lateral SN (l-SN)[4]. Furthermore, they demonstrated that K-ATP channels are necessary for NMDA-dependent bursting activity specifically in these m-SN neurons (**Fig. 1**).

The authors found that, in K-ATP channel global knockout (*Kir6.2*$^{-/-}$) mice, immunohistochemically identified dopaminergic neurons from m-SN, but not from l-SN or the VTA, displayed a decrease in bursting activity *in vivo*. Using a preparation of synaptically isolated m-SN neurons from wild-type mice, the authors observed that the application of NMDA, which has previously been shown to be necessary for bursting, was not sufficient to elicit robust bursting. However, bursting became apparent when application of NMDA was combined with pharmacological activation of K-ATP channels. Moreover, this bursting disappeared in the presence of a K-ATP channel inhibitor. The application of the K-ATP channel agonist did not change the firing pattern in *Kir6.2*$^{-/-}$ mice, and

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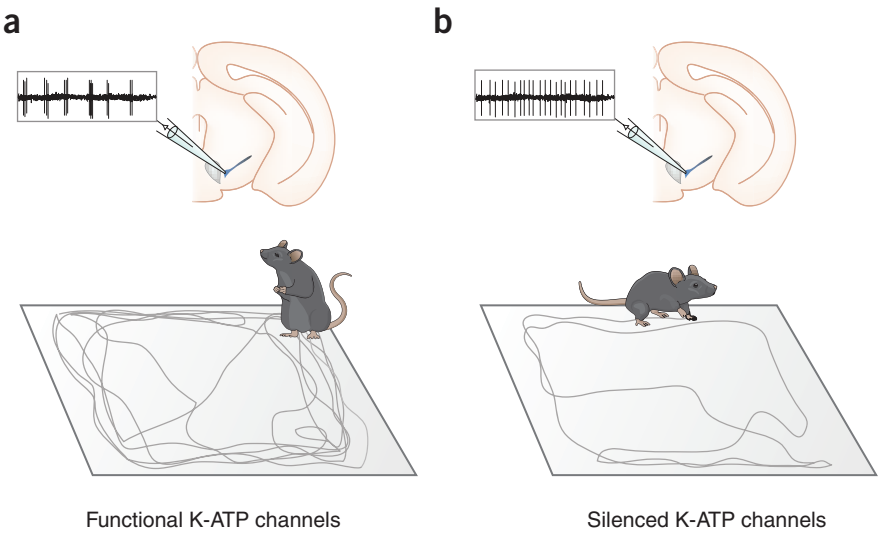

Figure 1 K-ATP channels mediate bursting of dopaminergic m-SN neurons and novelty-induced exploration. (**a**) Top, dopaminergic neurons from m-SN (brain region in blue) show bursty firing when K-ATP channels are functional. Bottom, mice with functional K-ATP channels in the m-SN (wild-type mice and mice with K-ATP channels silenced only in l-SN neurons) show normal exploration of a novel environment. (**b**) Top, when K-ATP channels are silenced, m-SN dopamine neurons lose their ability to fire in bursts. Bottom, mice with silenced K-ATP channels in m-SN neurons show reduced novelty-induced exploratory behavior.

the *Kir6.2*$^{-/-}$ mutation did not affect the firing of nondopaminergic neurons in SN.

The authors then recapitulated these findings using a virally mediated strategy to selectively silence K-ATP channels in SN neurons in adult mice[4]. Using adeno-associated viruses to express either dominant-negative or wild-type versions of Kir6.2 subunits in SN neurons, they found that expression of dominant-negative Kir6.2 silenced K-ATP channels in SN dopaminergic neurons and reduced the bursting activity of m-SN dopamine neurons *in vivo* (**Fig. 1b**).

Schiemann *et al.*[4] then examined the functional role of this K-ATP–mediated bursting in m-SN neurons[4]. m-SN neurons project to medial areas of the dorsal striatum that have been implicated in, among other things, the early phases of learning and in goal-directed behavior[7]. The authors found that *Kir6.2*$^{-/-}$ mice exhibited a decrease in locomotor activity during the first 2 min of exploring a novel environment, but not in subsequent sessions when the environment is no longer novel. Furthermore, virally mediated silencing of K-ATP channels in m-SN neurons, but not l-SN neurons, led to a selective reduction in novelty-induced locomotor activity (**Fig. 1b**). It will be interesting to investigate the function of this K-ATP–gated bursting in other dopamine-dependent behaviors mediated by the same circuits.

These findings are relevant for understanding the mechanisms that regulate the firing patterns of dopamine neurons, but they also bring new conceptual challenges. It had already been shown that NMDA receptors are necessary for the normal phasic response of dopaminergic neurons[8]. However, Schiemann *et al.*[4] found that, in a subgroup of SN dopaminergic neurons, K-ATP channels are necessary for NMDA receptor–dependent bursting, indicating that these neurons have a distinct functional regulation of spike patterns. This suggests that, along with differences in connectivity and anatomy (for example, m-SN neurons project to more medial regions of dorsal striatum and l-SN neurons to more lateral regions of dorsal striatum), there are also characteristic molecular and functional signatures for subpopulations of dopamine neurons within the SN. These findings also encourage new anatomical studies to determine whether, as has been found for VTA and SN[9,10], m-SN and l-SN dopamine neurons are part of distinct circuits that not only project to different areas, but also receive inputs from different brain regions.

Moreover, the neurophysiological and behavioral results reported in this study invite new hypotheses and experiments that could shed light on the mechanisms by which dopamine neurons change their activity during different behaviors. For example, K-ATP channels are sensitive to the metabolic status of cells and can link the energy levels of neurons and their excitability[11]. Given the sensitivity of these channels to metabolic changes[12], one hypothesis could be that some m-SN neurons are particular sensitive to food deprivation or other states that change available glucose. This could explain why food deprivation leads to changes in motivation[13] and operant reinforcement[14].

Finally, the authors establish a possible relation between their findings and the etiology of Parkinson's disease. SN neurons are lost in Parkinson's disease, but the mechanisms that lead to this loss are not completely understood. Notably, a previous study from the same laboratory found that knocking out K-ATP channels in two different animal models of Parkinson's disease led to a partial rescue of SN neuron loss[15]. Schiemann *et al.*[4] report an increased expression of K-ATP channels in surviving dopaminergic neurons in post-mortem samples from patients with Parkinson's disease. Furthermore, they compared the activity of SN dopaminergic neurons recorded intraoperatively from patients with Parkinson's disease with the activity of control dopamine neurons from other species (as it is extremely difficult to obtain data from healthy humans) and found that SN dopaminergic neurons from patients had a higher proportion of spikes fired in bursts. Further studies will be needed to determine whether K-ATP–mediated bursting of m-SN neurons is related to the loss of dopaminergic neurons observed in Parkinson's disease.

Schiemann *et al.*'s results[4] implicate a metabolic state–sensitive channel in the bursting of a specific population of dopaminergic neurons in health and disease and highlight the potential mechanistic and functional diversity of midbrain dopaminergic neurons.

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